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L11  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2003:719484  CAPLUS
DOCUMENT NUMBER:          139:247494
TITLE:                    Method and system for separation and
                          purification of narcotic alkaloids using
                          reversed-phase preparative
                          chromatography
INVENTOR(S):              Antonini, Enrico A.
PATENT ASSIGNEE(S):       Mallinckrodt Inc., USA
SOURCE:                   PCT Int. Appl., 73 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2003074526         A2    20030912    WO 2003-US4498          20030218
     WO 2003074526         A3    20031204
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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     CA 2477739            A1    20030912    CA 2003-2477739         20030218
     AU 2003216279         A1    20030916    AU 2003-216279          20030218
     EP 1487838            A2    20041222    EP 2003-743676          20030218
     EP 1487838            B1    20080903
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     CN 1639166            A     20050713    CN 2003-804869          20030218
     JP 2005522460         T     20050728    JP 2003-572994          20030218
     AT 407136             T     20080915    AT 2003-743676          20030218
     ES 2312798            T3    20090301    ES 2003-743676          20030218
     US 20050182257        A1    20050818    US 2004-501353          20040714
     MX 2004008213         A     20050516    MX 2004-8213            20040824
     IN 2004CN01890        A     20070720    IN 2004-CN1890          20040825
     ZA 2004005932         A     20060531    ZA 2004-5932            20060316
PRIORITY APPLN. INFO.:                       US 2002-360321P     P   20020228
                                             US 2002-434597P     P   20021216
                                             WO 2003-US4498      W   20030218
AB   Narcotic alkaloids are separated by feeding a crude alkaloids solution into a
     chromatog. column containing a compressed reversed-phase stationary phase,
     applying an acidic solution (pH 2-5) to the chromatog. column to recover
     eluates containing morphine, codeine, oripavine, papaverine, thebaine, and
     narcotine, resp. from the chromatog. column, adding a caustic solution to
     resp. eluate to precipitate and sep. the alkaloid.  The mobile phase can be
     acetonitrile, water, ethanol, and iso-propanol.  The stationary phase can
     consist of chemical modified silica, titania, zirconia, or a polymer.  The
     acidic solution can contain acetic acid, formic acid, oxalic acid, succinic
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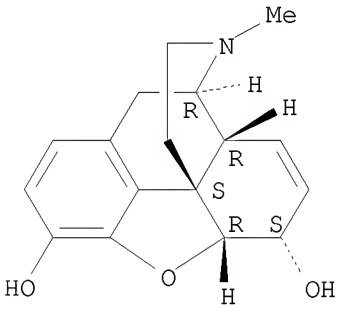
acid, lactic acid, and tartaric acid. A reagent can be added to the crude alkaloid solution, such as triethylamine, tetrabutylammonium hydrogen sulfate, sodium dodecyl sulfate, sodium heptane sulfonate, or ammonium sulfate. The caustic solution can contain NaOH, KOH, NH4OH, and carbonate salts of alkali metals. A system for separating at least one narcotic alkaloid consists of a chromatog. column having a fluid chamber and a media chamber, with a diameter of ≥ 5 cm having an inlet connected to a liquid tank via a 1st valve, an outlet connected to an eluate tank via a 2nd valve, and a fluid purge orifice connected to the outlet via a 3rd valve, a double-acting piston that includes a plate, having an upper face and a lower face, and a rod. The piston is located within the chromatog. column for compressing the stationary phase between the lower face of the plate and the bottom of the chromatog. column. A hydraulic pump provides fluid to the double-acting piston.

IT 57-27-2P, Morphine, preparation
RL: PUR (Purification or recovery); PREP (Preparation)
(separation and purification of narcotic alkaloids using reversed-phase preparative chromatog.)

RN 57-27-2 CAPLUS

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1994:686684 CAPLUS

DOCUMENT NUMBER: 121:286684

ORIGINAL REFERENCE NO.: 121:52227a

TITLE: High-performance liquid chromatography for small-scale studies of drug stability

AUTHOR(S): Hagan, Robert L.

CORPORATE SOURCE: Analytical Research Laboratory, David Grant USAF Medical Center, Travis Air Force Base, CA, 94535-1800, USA

SOURCE: American Journal of Hospital Pharmacy (1994), 51(17), 2162-75
CODEN: AJHPA9; ISSN: 0002-9289

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 10 refs. The fundamentals of high-performance liquid chromatog. (HPLC), as applied in small-scale studies of drug stability, are presented. Chromatog. is the separation of a complex mixture into its individual compds. through partitioning between a mobile phase and a stationary phase. A high-performance liquid chromatog. consists of

mobile-phase reservoirs, pumps, a mixer to mix the solvents, a valve into which the sample is injected, a guard column, a column containing the stationary phase, a detector, and a recorder. Once compds. have been separated in the column, they pass into the detector, where an electronic signal corresponding to the amount of compound present is recorded as a peak in a chromatogram. The most common detection method is UV and visible light spectroscopy. Key concepts in HPLC theory are retention time, the time from injection of the sample to detection of a peak; capacity factor, a measure of retention corrected for the elution of an unretained compound; resolution, a measure of how well two peaks are separated; the selectivity of the method; efficiency, or resolving power; and the degree of symmetry of the peaks produced. Most HPLC sepns. are performed in the reverse-phase mode, which involves a non-polar stationary phase and a largely polar mobile phase. Other modes are normal phase, ion exchange, and size exclusion. Before a drug stability study is carried out, an HPLC method must be developed that suits the needs of the proposed experiment A thorough literature search is essential. Literature procedures serve as useful starting points but may require a great deal of manipulation. After the HPLC separation has been performed, it is necessary to validate the method used. It must be proved that the method is stability indicating, that the chromatog. stds. were properly prepared, that the standard curve is acceptable, and that the method is both precise and accurate. Pharmacists who ensure that reliable, reproducible HPLC methods are used throughout studies of drug stability will obtain sound data that may be of great value in pharmacy practice.

L11 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:107 CAPLUS
DOCUMENT NUMBER: 98:107
ORIGINAL REFERENCE NO.: 98:15a,18a
TITLE: Analysis of morphine in serum by high performance liquid chromatography with amperometric detection
AUTHOR(S): Vandenberghe, H.; MacLeod, S. M.; Chinyanga, H.; Soldin, S. J.
CORPORATE SOURCE: Dep. Clin. Biochem., Univ. Toronto, Toronto, ON, Can.
SOURCE: Therapeutic Drug Monitoring (1982), 4(3), 307-14
CODEN: TDMODV; ISSN: 0163-4356
DOCUMENT TYPE: Journal
LANGUAGE: English
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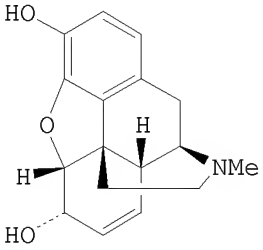

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AB A rapid and sensitive micromethod for morphine (I) [57-27-2] determination in serum or plasma using high performance liquid chromatog. with electrochem. detection is described. The separation of morphine and the internal standard, 5-hydroxyquinoline, from interfering compds. present in

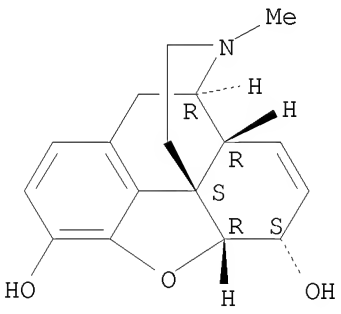
plasma was achieved by paired-ion reverse phase chromatog. using a 70 mM phosphate buffer at pH 5.80. The flow rate was 1 mL/min. Oxidation of morphine and the internal standard was obtained at a potential of 0.60 V. Only 100 μL of serum or plasma was required. Anal. recoveries for morphine and 5-hydroxyquinoline were determined as 78% and 63%, resp. The between-day precision of serum samples containing 250, 100, and 25 μg/L of morphine was 6.5%, 5.2%, and 9.5% resp. The detection limit was 1 μg/L at a sensitivity of 5 nA/V. Children between the ages of 0 and 5 yr received a bolus of morphine of 11 μg/kg, followed by an infusion of 2 μg/kg/min during surgery. The time-concentration curves demonstrated an initial rapid fall in morphine concentration with subsequent attainment of a steady state concentration of approx. 90 μg/L after 1 h. This concentration would be expected to produce optimal analgesia in conscious patients.

IT 57-27-2, analysis
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood by high-performance liquid chromatog., pharmacokinetics in children in relation to)

RN 57-27-2 CAPLUS

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, (5α,6α)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1981:127428 CAPLUS

DOCUMENT NUMBER: 94:127428

ORIGINAL REFERENCE NO.: 94:20751a,20754a

TITLE: Quantitative determination of opium alkaloids by liquid chromatographic methods

AUTHOR(S): Matantseva, E. F.; Gladyshev, P. P.; Goryaev, M. I.; Bektenova, G. A.

CORPORATE SOURCE: Inst. Khim. Nauk, Alma-Ata, USSR

SOURCE: Khimiya Prirodnykh Soedinenii (1980), (5), 730-1
CODEN: KPSUAR; ISSN: 0023-1150

DOCUMENT TYPE: Journal

LANGUAGE: Russian

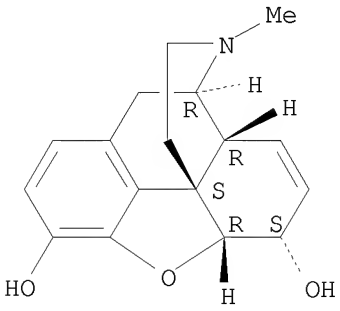
AB Ion-exchange and reverse-phase chromatog. is described for separating phenolic and nonphenolic alkaloids from Papaver somniferum capsules using P-cellulose, Bondapak CX/Corasil, and Bondapak C18/Corasil adsorbents. The eluents for the 3 adsorbents were 0.1N Na phosphate buffer (pH 7.5), 0.1N Ca phosphate buffer with 30% MeCN (pH 4.8), and 0.1N Ca phosphate buffer with 30% MeCN (pH 7.5). The wave length used for the monitoring these alkaloids was 254 nm. The alkaloids separated were morphine [57-27-2], codeine [76-57-3], narcotine

[128-62-1], thebaine [115-37-7], papaverine [58-74-2], narcotoline [521-40-4], oxydimorphine [125-24-6], narceine [131-28-2], and laudanidine [301-21-3].

IT 57-27-2, analysis
RL: ANST (Analytical study)
(separation of, from opium alkaloids, by ion-exchange reverse-phase chromatog.)

RN 57-27-2 CAPLUS
CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, (5α,6α)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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E MORPHINE/CN
L1 1 S E3

FILE 'CAPLUS' ENTERED AT 10:05:20 ON 12 JUN 2009
L2 29660 S L1
L3 1221125 S SEPARATION OR PURIFICATION
L4 956 S L2 AND L3
L5 3586 S REVERSE PHASE CHROMATOGRAPHY OR PREPARATIVE CHROMATOGRAPHY
L6 3 S L4 AND L5
L7 48 S NON-POLAR STATIONARY PHASE
L8 66 S POLAR MOBILE PHASE
L9 1 S L7 AND L8
L10 0 S L2 AND L9
L11 4 S L6 OR L9

=> d l1
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y

THE ESTIMATED COST FOR THIS REQUEST IS 2.05 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 57-27-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-

(5α,6α)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morphinan-3,6α-diol, 7,8-didehydro-4,5α-epoxy-17-methyl- (8CI)
OTHER NAMES:
CN (-)-Morphine
CN Aguettant
CN DepoDur
CN Dinamorf
CN Dulcontin
CN Duromorph
CN l-Morphine
CN M-Eslon
CN Meconium
CN Morphia
CN Morphin
CN Morphina
CN Morphine
CN Morphinism
CN Morphinum
CN Morphium
CN MS Contin
CN Nepenthe
CN Ospalivina
CN Sevredol
CN Statex SR
FS STEREOSEARCH
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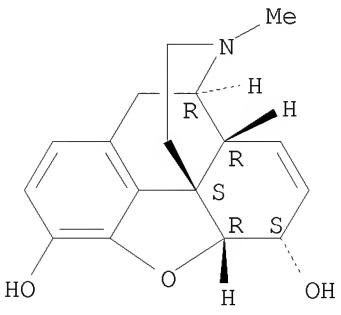
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSPATENTS, IMSPRODUCT, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

29614 REFERENCES IN FILE CA (1907 TO DATE)
350 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29657 REFERENCES IN FILE CAPLUS (1907 TO DATE)

10/501,353

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